**#617P** 

# Genomic profiling of circulating tumor DNA in advanced genitourinary cancer patients: SCRUM-Japan MONSTAR SCREEN Nationwide Cancer Genome Screening Project

Taigo Kato<sup>1</sup>, Nobuaki Matsubara<sup>2,</sup> Takao Fujisawa<sup>3</sup>, Masaki Shiota<sup>4</sup>, Masatoshi Horasawa<sup>8</sup>, Naomi Kuramoto<sup>8</sup> Yoshiaki Nakamura<sup>8</sup>, Hiroya Taniguchi<sup>8</sup>, Takayuki Yoshino<sup>9</sup>, Norio Nonomura<sup>1</sup>

<sup>1</sup>Urology, Osaka University Graduate School of Medical Oncology, National Cancer Center Hospital East; <sup>3</sup>Head and Neck Medical Oncology, National Cancer Center Hospital East; <sup>3</sup>Head and Neck Medical Oncology, National Cancer Center Hospital East; <sup>4</sup>Urology, National Cancer Center Hospital Ea Medicine; <sup>6</sup>Urology, Keio University School of Medical Center Hospital East; <sup>9</sup>Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East; <sup>9</sup>Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East; <sup>9</sup>Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East; <sup>9</sup>Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East; <sup>9</sup>Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East; <sup>9</sup>Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East; <sup>9</sup>Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East; <sup>9</sup>Gastroenterology and Gastroenterology and Gastroenterology and Gastroenterology, National Cancer Center Hospital East; <sup>9</sup>Gastroenterology and Gastroenterology and Gastroenterology, National Cancer Center Hospital East; <sup>9</sup>Gastroenterology and Gastroenterology, National Cancer Center Hospital East; <sup>9</sup>Gastroenterology, National Centerology, National Centerology, National Centerology, National Ce

#### Abstract

#### Induction & Objective

Circulating tumor DNA (ctDNA) is an emerging resource for the diagnosis and prognosis of various types of cancer. However, characteristics and clinical utility of ctDNA is still largely unknown, especially in patients with genitourinary (GU) cancers.

#### Methods

SCRUM-Japan consortium of Nationwide Cancer Genome Screening Project has started MONSTAR-SCREEN project which evaluates ctDNA for patients with advanced solid tumors since Apr 2019 in Japan. We collected plasma and tumor samples in patients with prostate cancer (PC), urothelial carcinoma (UC), and renal cell carcinoma (RCC). Plasma ctDNA and tumor genomic DNA were analyzed by a NGS-based ctDNA assay, Foundation One<sup>®</sup> Liquid (F1L) and tissue-based panel, Foundation One<sup>®</sup> CDx (F1CDx), respectively.

#### Results

As of Dec 2020, 1225 patients with advanced solid tumors were enrolled in MONSTAR-SCREEN. Among them, we analyzed 226 ctDNA samples of advanced GU cancers (95 PC, 73 UC, and 58 RCC) and compared the feature in GU cancers with that in non-GU cancers. The level of ctDNA in GU cancers was significantly lower compared to that in non-GU cancers (median 1.1% vs. 3.2%, p = 0.0015). Although UC possessed the highest median blood tumor mutation burden (bTMB) in all cancers (4.39), there was no significant bTMB difference between GU cancers and non-GU cancers (2.63 vs. 2.63, P = 0.995). Interestingly, the mutation rate in genes related to DNA damage response pathway tended to be higher in GU cancers compared to that in non-GU cancers (24.3 % vs. 19.1%, P =0.080). When we focus on other major oncogenic signaling pathways such as PI3K, MAPK and Wnt-signal pathway, we found that related genes in these pathways were less frequently altered in GU cancer versus non-GU cancers (p = 9.3E-4, p = 1.3E-10 and p = 1.3E-102.6E-6, respectively). We also assessed concordance between liquid biopsy and tumor tissue-based sequencing and found that 47% of detected variants in F1L were overlapped with that in F1CDx.

#### Conclusions

For the first time, we performed comprehensive genomic profiling of ctDNA in GU cancers. We further evaluate ctDNA profiling before and after starting cancer treatments and connect these data to clinical trials.

## **Background & Objectives**

- •Analysis of circulating tumor DNA (ctDNA) has been utilized in patients with advanced genitourinary (GU) cancers for identification of genomic alterations for target therapy.
- •However, the characteristics of ctDNA genomic alterations of GU cancers compared to non-GU cancers remain unclear.
- •We aimed to reveal genomic landscape of ctDNA in GU cancers and compared the feature in GU cancers with that in non-GU cancers.

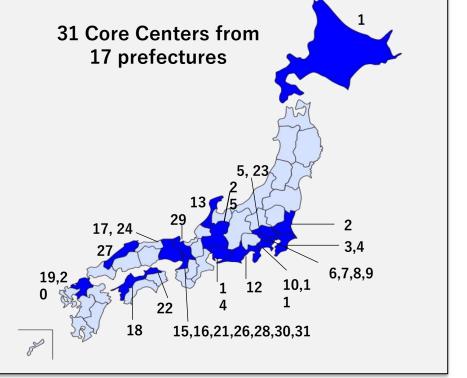
## **SCRUM-Japan MONSTAR-SCREEN**

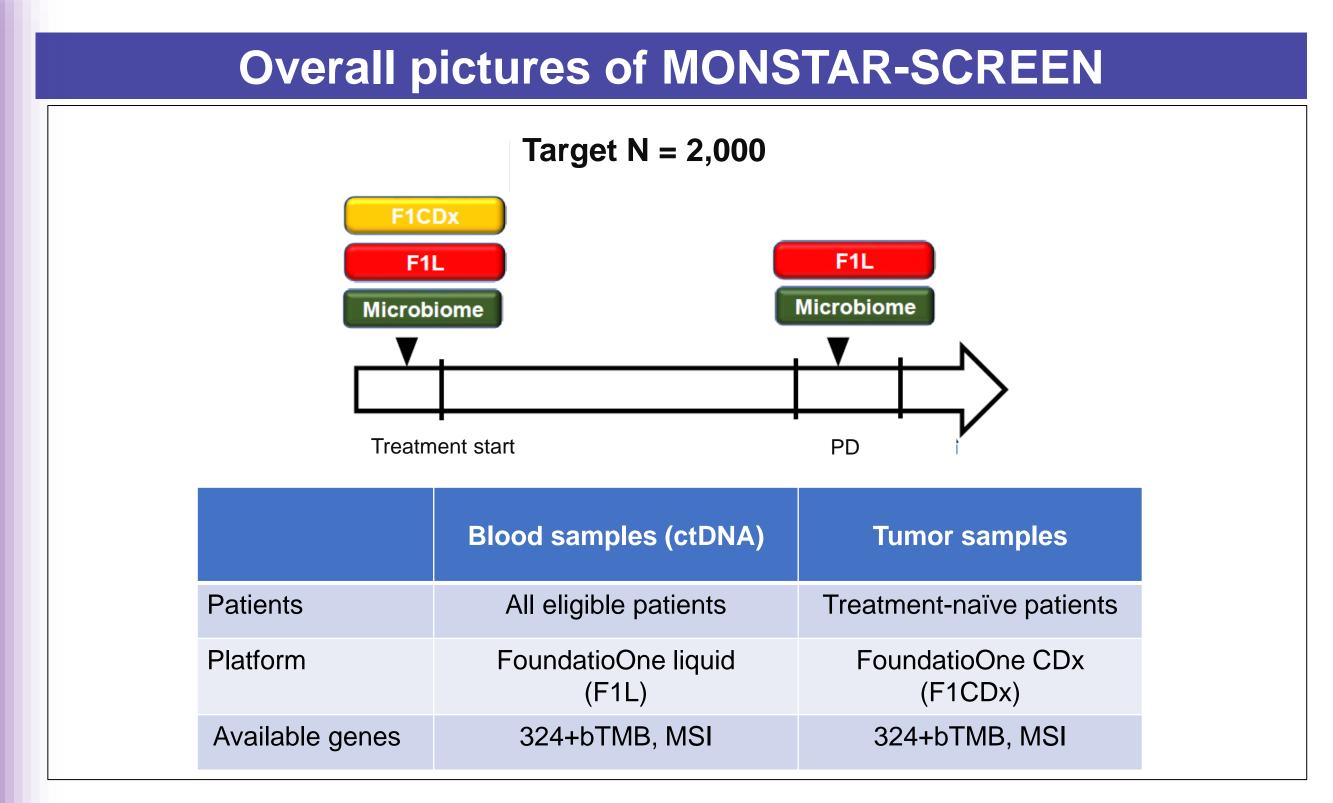
- A nationwide ctDNA screening project for patients with advanced solid tumors in Japan since 2019
- MONSTAR-Urology group launched their work first with 6 high volume centers and now has been expanding

okkaido University Hosp University of Tsukuba 3.National Cancer Center Hospital E 4.Chiba Cancer Center

- Saitama Cancer Center
- 6.National Cancer Center Hospital 7.Keio University School of Medicine
- 8.Kyorin University Hospital 9. The Cancer Institute Hospital of JFCR
- 10. St. Marianna University School of Medicine
- 11. Kanagawa Cancer Center
- 12. Shizuoka Cancer Center 13. Kanazawa University
- 14. Aichi Cancer Center Hospital
- 15. Osaka University Graduate School of Medicine 16. Kindai University

- 9. National Hospital Organization Kyushu Cancer Center
- 20. Kyushu University 1. National Hospital Organization Osaka National Hospital
- 22. Kagawa University
- 23. Saitama Medical University International Medical Center 24. Kobe City Medical Center General Hospital
- 25. Gifu University Hospital 26. Osaka Medical College Hospital
- 27. Shimane Prefectural Central Hospital
- 28. Kansai Medical University Hospital
- 29. Kyoto Katsura Hospital 30. Osaka International Cancer Institute
- 31. Osaka General Medical Center

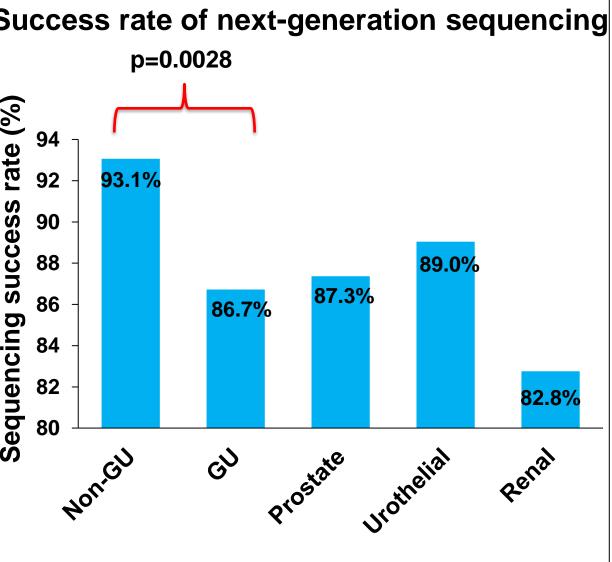




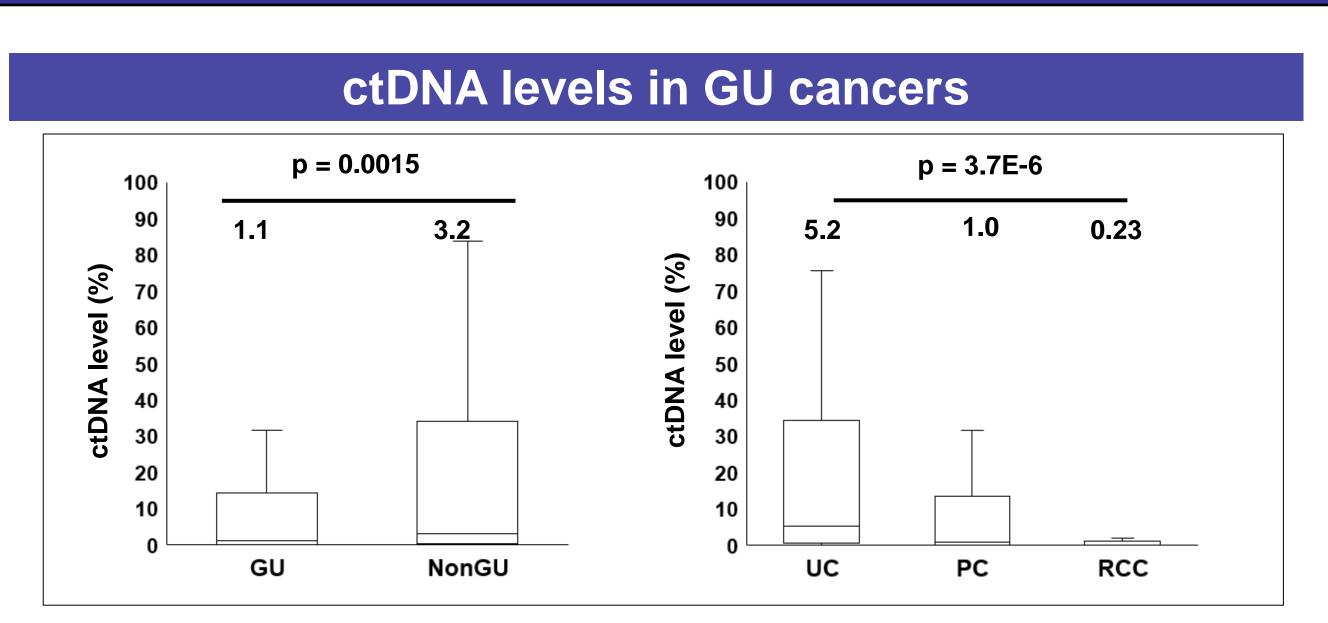
- MONSTAR-SCREEN project consists of 4 cohorts such as chemo-naïve advanced cancer patients or patients who receive immunotherapy.
- The project first performs tissue-based next-generation sequencing analysis and further evaluate ctDNA as well as microbiome before and after starting cancer treatments to explore factors associated with responsiveness or refractoriness to treatment.

## Distribution of cancer types in MONSTAR-SCREEN (Interim analysis)

FIL	., Pretr	eatment (N = 120	6)	Succe	ss ra
GU (N =	226)	Non-GU (N =	980)	•	k
Prostate	95	Gastrointestinal	326	rate (%)	Γ
Urothelial	73	Hepatobiliary and Pancreatic	252		93.1
Renal	58	Breast	136	0 0 0 0 88 -	
		Head and Neck	106	Seduencing success 88 - 86 - 84 - 82 - 80 -	
		Gynecologic	103	0 - 84	
		Skin	43	90 82 -	
		NET/C	13		
		CUP	1	0)	onGU

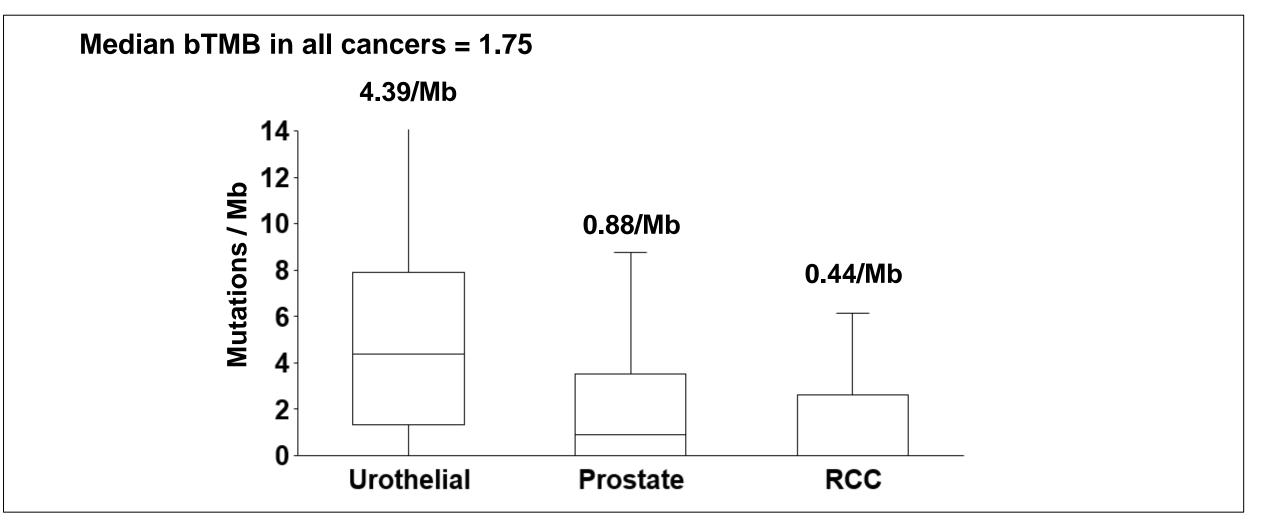


- In May this year, MONSTAR-SCREEN project conducted interim analysis of ctDNA from 1,206 pre-treatment cases.
- We enrolled 226 GU cancers including 95 prostate cancers, 73 urothelial carcinomas and 58 renal cell carcinomas, whereas non-GU cancers mainly consist of GI and hepatobiliary and pancreatic cancers.
- The success rate of next-generation sequencing in prostate cancer and urothelial carcinoma were 85.7% and 82.4%, respectively. Renal cell carcinoma had a low success rate of 72.2%. As a result, the success rate of ctDNA was significantly lower in GU cancers than non-GU cancers.



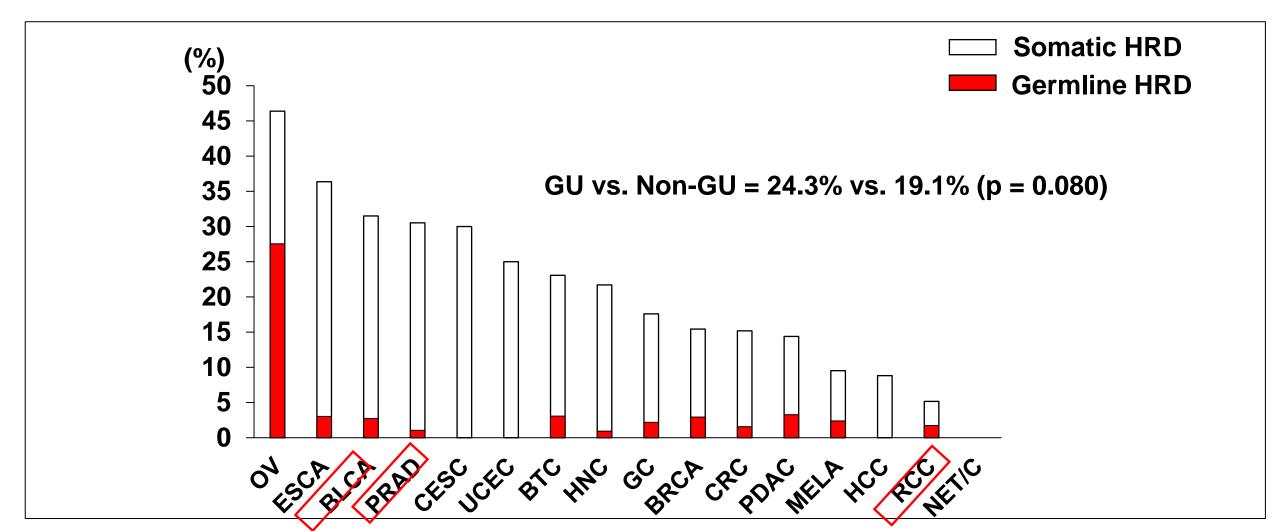
- Urothelial carcinoma had highest ctDNA level around 5.2% in all tumor types.
- In total, GU cancers had significantly higher ctDNA level than non-GU cancers (p = 0.0015).

## Median blood tumor mutational burden (bTMB)

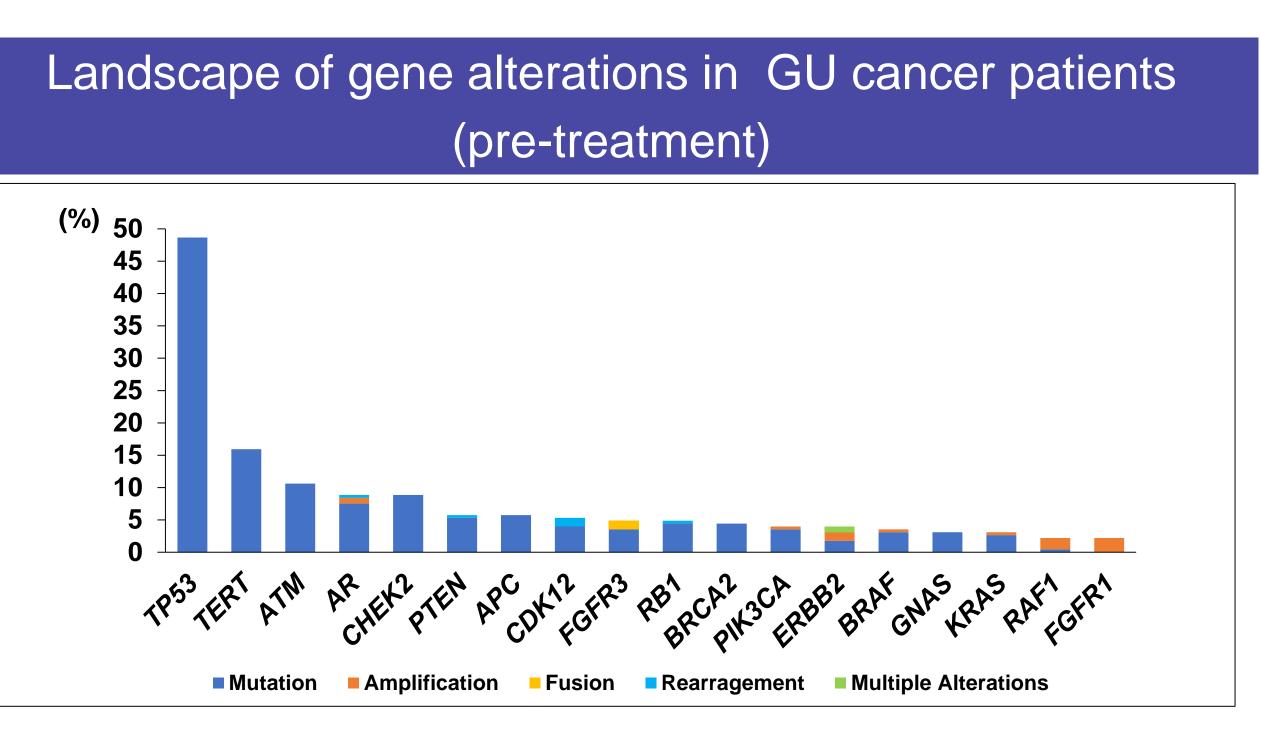


F1L possess the algorism to predict tumor mutation burden (bTMB) using blood samples. Median bTMB in all cancers was 1.75 and interestingly, urothelial carcinoma possessed the highest bTMB in all solid cancers.

#### Prevalence of homologous recombination deficiency



The mutation rate of homologous recombination repair (HRR) gene is high around 20-50% in ovarian, esophageal, and urothelial carcinoma. Interestingly, GU cancers tended to have higher HRR mutation rate than non-GU cancers.



 This slide shows the landscape of gene alterations in pre-treatment GU cancers. TP53, TERT, and ATM, CDK12 and CHEK2 (these genes are HRR genes) were frequently found in pre-treatment liquid biopsy.

		RTK								МАРК							РІЗК						HRD							Cell Cycle p53					Epi Gen								
		ERBB2	EGFR	FGFR1	FGFR2	FGFR3	MET	ERRF11	КІТ	RET	KRAS	NRAS	HRAS	NF1	BRAF	ARAF	RAF1	MAP2K1	PIK3CA	PTEN	AKT1	STK11	MTOR	BRCA2	BRCA1	ATM	CHEK2	CDK12	PALB2	<b>CDKN2A</b>	RB1	CCND1	TP53	APC	CTNNB1	1H01	IDH2	TERT	CDH1	ESR1	GNAS	AR	12000
	solid nor	4	3	2	1	2	1	1	1	0	19	1	1	5	4	0	1	1	13	7	1	2	1	5	2	9	6	2	1	4	5	1	68	20	2	0	0	7	3	3	3	2	
GU	PC	2	2	2	0	1	2	0	0	0	3	0	0	1	4	0	0	1	1	5	1	0	0	6	0	12	9	9	1	1	4	0	34	11	1	0	0	4	2	0	1	21	(
GU	UC	10	3	4	0	14	0	0	0	0	5	0	5	3	5	0	7	0	10	8	0	0	0	5	1	15	15	4	3	1	10	0	88	4	1	0	0	38	0	0	3	0	(
GU	RCC	0	0	0	0	0	0	0	0	0	0	2	0	2	0	0	0	0	2	3	0	0	7	0	2	3	0	0	0	2	0	2	24	0	0	0	0	7	0	0	7	0	(

When we focus on MAPK, PI3K, and Wnt pathways, representative genes in all pathways were less frequently altered in GU cancer versus non-GU cancers.

## Conclusions

- The success rate of sequencing ctDNA was significantly lower in GU cancers than non-GU cancers, especially RCC had low success rate.
- Alterations in DNA damage response pathway tended to be more frequent in GU cancers than in non-GU cancers (p = 0.08).
- Other major oncogenic signaling pathways such as MAPK, PI3K, and Wnt pathway, were less frequently altered in GU cancer versus non-GU cancers.

## **Disclosure statement**

No potential conflicts were disclosed.